Physiologically based pharmacokinetic model to predict drug-drug interaction in patients receiving antiretroviral and antineoplastic therapies

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Background

- Incidence of non-AIDS defining malignancies is increasing.
- Administration of chemotherapy is challenging due to drug-drug interactions with cART.
  - Specific data on DDI remain scant
- Erlotinib (ERL) and gefitinib (GEF) are two EGFR inhibitors used to treat patients with non-small cell lung cancer.
  - ERL is dosed at 150 mg qd (MTD)
  - GEF is dosed at 250 mg qd (1/3 MTD)
  - ERL and GEF are metabolized by CYP3A4

Objective

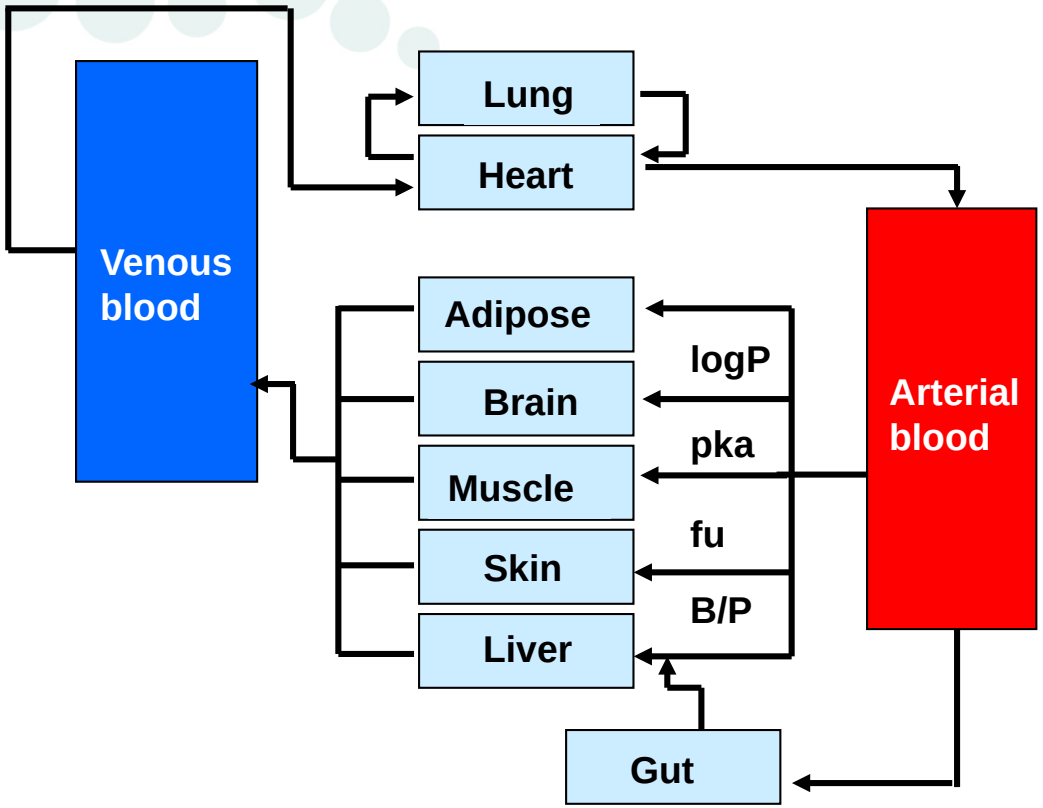
To evaluate DDIs between ERL or GEF and antiretroviral drugs including ritonavir (RTV), efavirenz (EFV) or etravirine (ETR) using a PBPK model, and to hypothesize potential dose adjustments to overcome these DDIs.

PBPK modelling

DRUG PROPERTIES

PATIENTS CHARACTERISTICS

TRIAL DESIGN



New formulations

PK special populations

Drug-drug interactions

Methods

1.- Validation of PBPK models for each drug ERL, GEF, RTV, EFV, ETR, MVC and MDZ given separately

2.- Validation of DDI models with CYP3A4 probe drugs

Midazolam +/- RTV

Maraviroc +/- EFV / ETR

3.- Simulate concentrations of ERL/GEF +/- ARVs

4.- Predict dose adjustments to overcome DDIs

Methods

- **Simbiology** (in MATLAB, version 2013b)
- **Virtual cohort of 50 healthy volunteers**
- **Drugs dosing (14 days)**
  - ERL 150 mg qd
  - GEF 250 mg qd
  - RTV 100 mg qd
  - EFV 600 mg qd
  - ETR 200 mg bid
  - MDZ 2 mg (sd)
  - MVC 300 mg bid
- **Model validation**

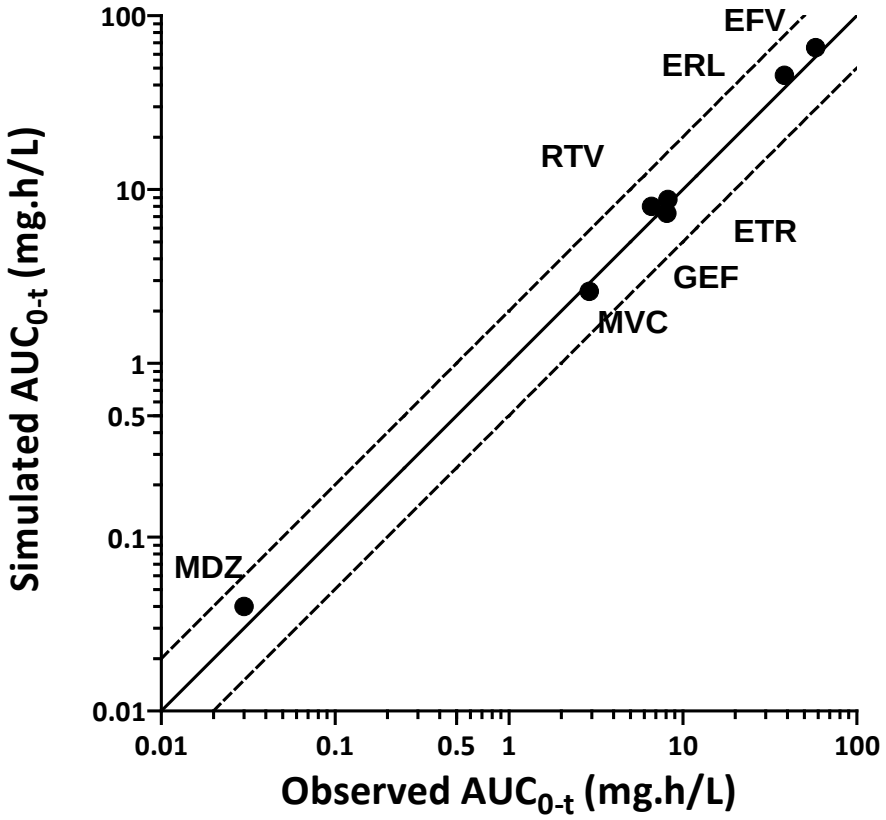
  Simulated data vs. reference values
- **Evaluation of DDI**

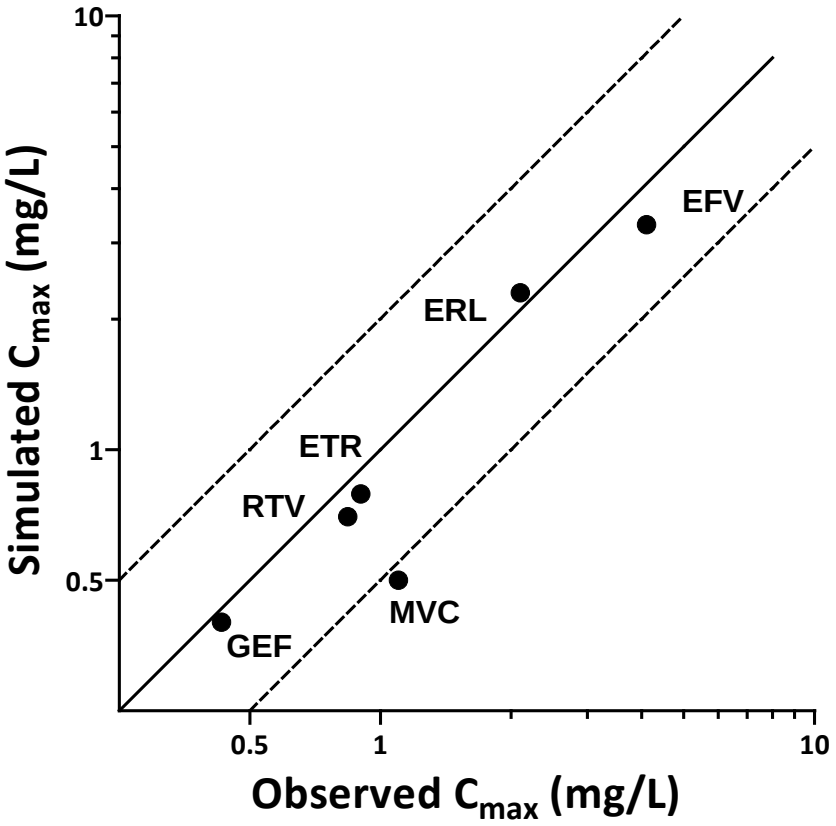
  GMR (90%CI)

Methods. In vitro parameters

	ERL	GEF	RTV	ETR	EFV	MVC	MDZ
pKa	5.6	7.2	3.5	3.75	10.2	7.3	6.0
logP	2.7	3.2	3.6	5.2	4.6	2.4	2.95
fu	0.05	0.03	0.04	0.01	0.02	0.25	0.037
B/P	0.88	0.76	0.58	0.70	0.74	0.59	0.55
Clint (mL/min/pmol)	CYP3A4 0.09 CYP3A5 0.05 CYP2D6 0.04 CYP1A2 0.03 CYP1A1 0.02	CYP 3A4 0.809 CYP2D6 0.879	CYP3A4 20.14 CYP 2D6 0.93	CYP2C19 0.75 CYP3A4 0.012	CYP2B6 0.55 CYP2A6 0.08 CYP3A5 0.03 CYP3A4 0.007	CYP3A4 1.7 (ISEF 0.2)	CYP3A4 2
Induction data			CYP3A4 Indmax 13.4 Ind50 0.44μM	CYP3A4 Indmax 2.5	CYP3A4 Indmax 5.7 Ind50 0.8 μM CYP2B6 Indmax 6.5 Ind50 3.9 μM		
Inibition CYP3A4			Ki 0.04 μM Kinact 0.3 min^{-1}		Ki 20 μM		

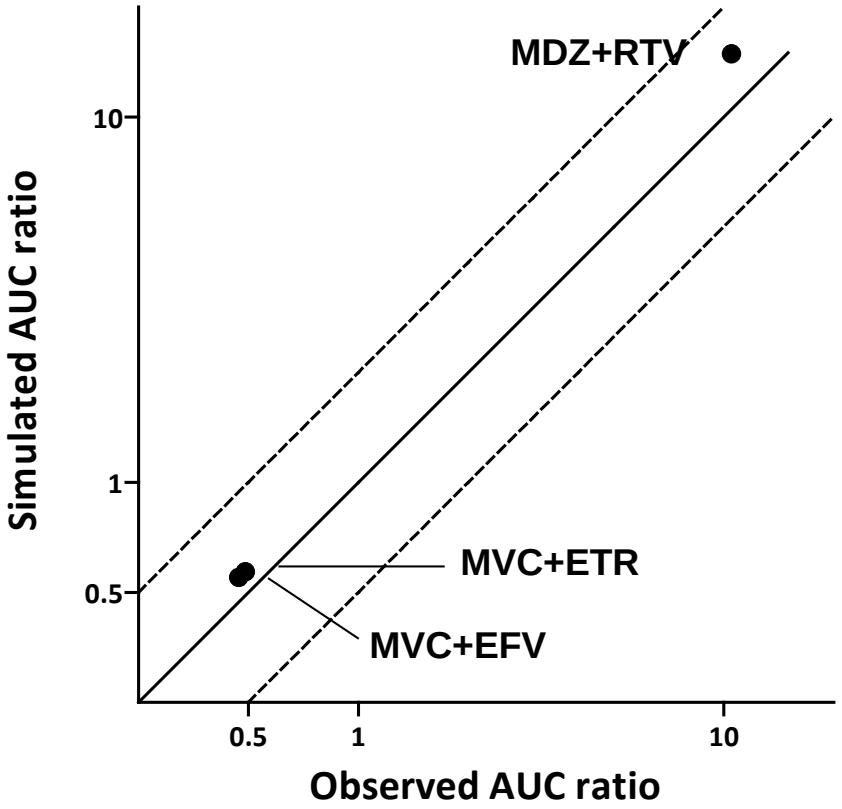
Model validation for each drug separately

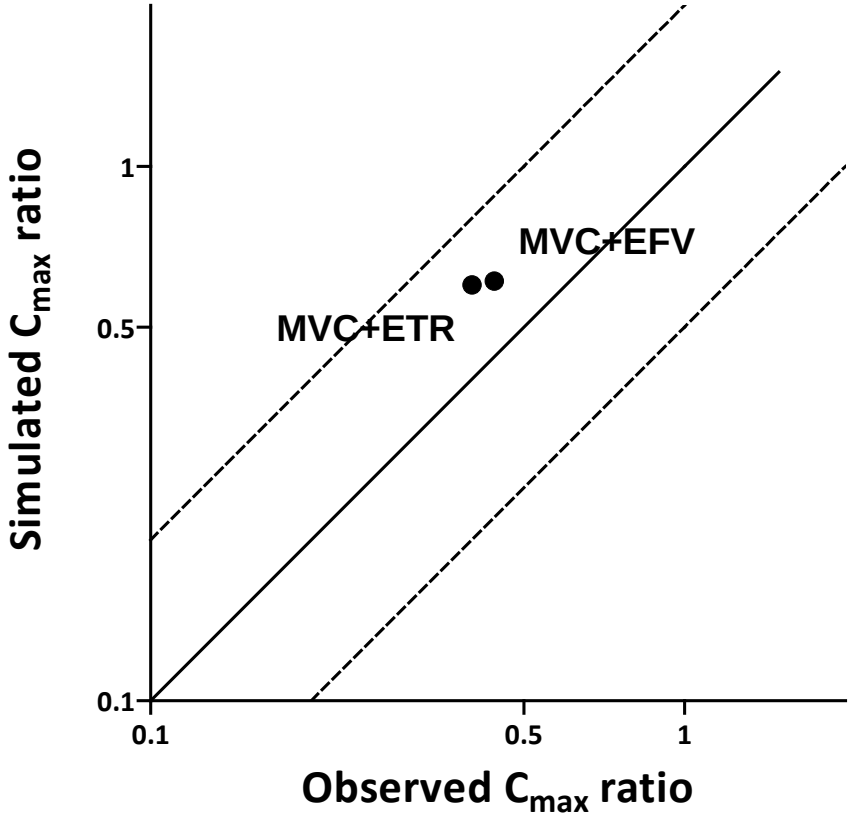




Hidalgo et al. J Clin Oncology 2001; Adjei et al. Clin Canc Res 2007; www.hiv-drug-interactions.org; Efavirenz product information; Schöller-Gyüre et al. Clin Pharmacokinet 2009. Kirby et al. Drug Metab Disp 2011. Kakuda et al. Antimicrob Agents Chemother 2011

Model validation for CYP3A4 probe DDIs



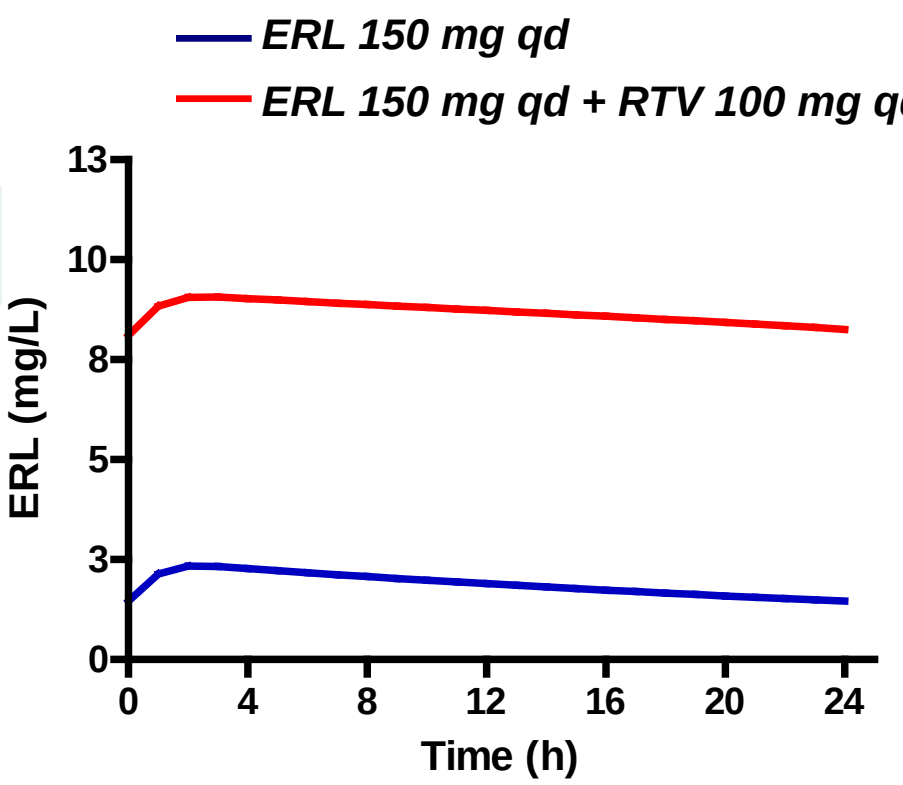


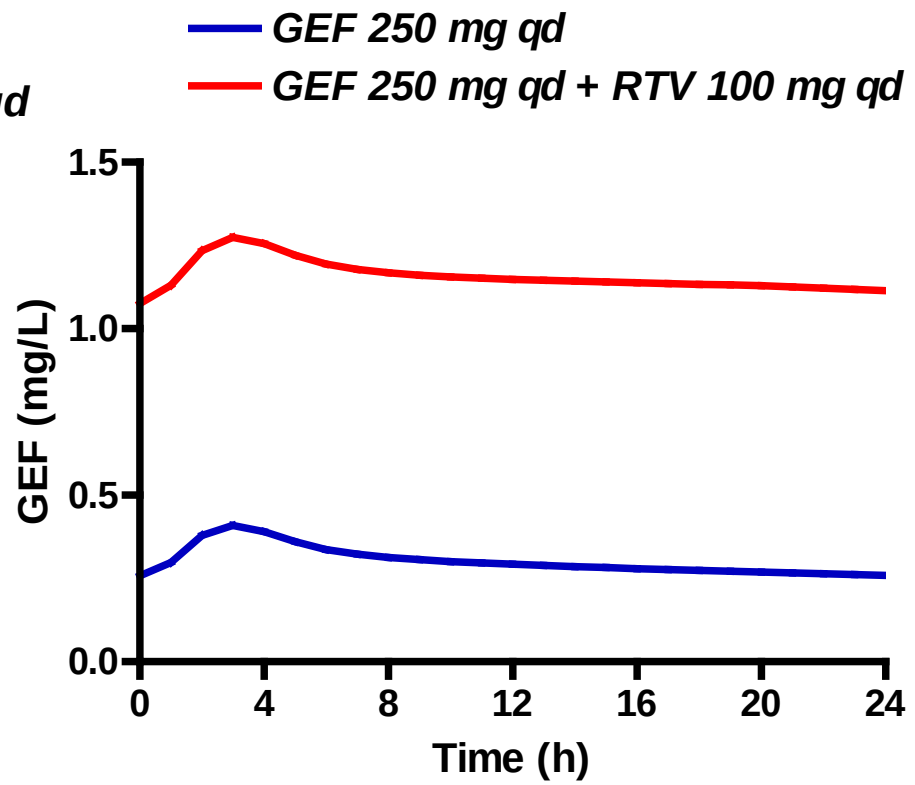
Kirby et al. Drug Metab Disp 2011

Abel et al. Br J Clin Pharmacol 2008

Kakuda et al. AAC 2011

Erlotinib/Gefitinib & RTV

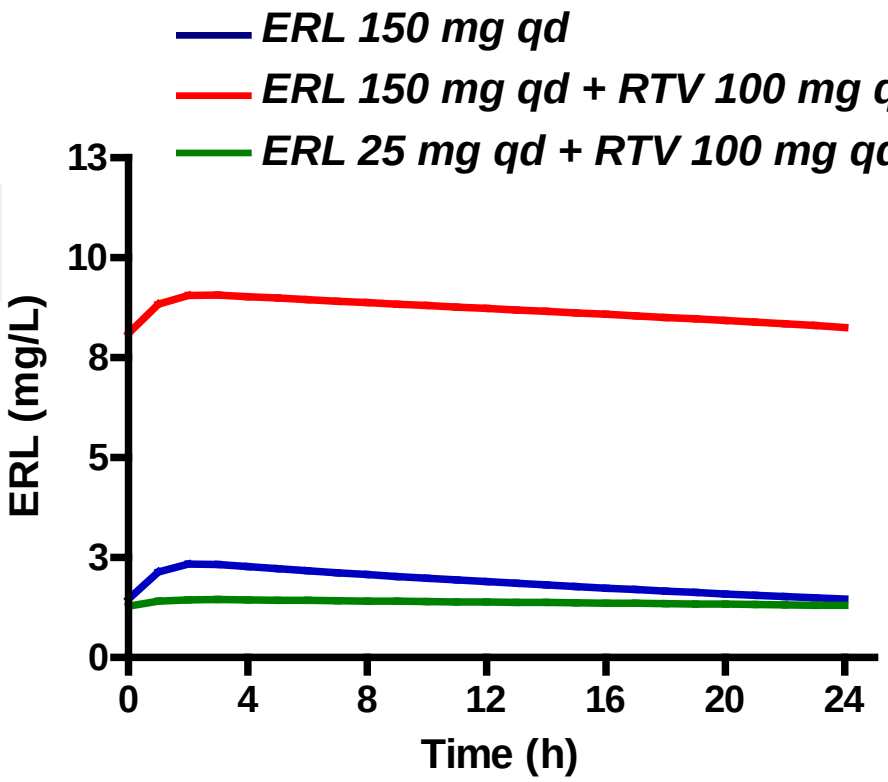


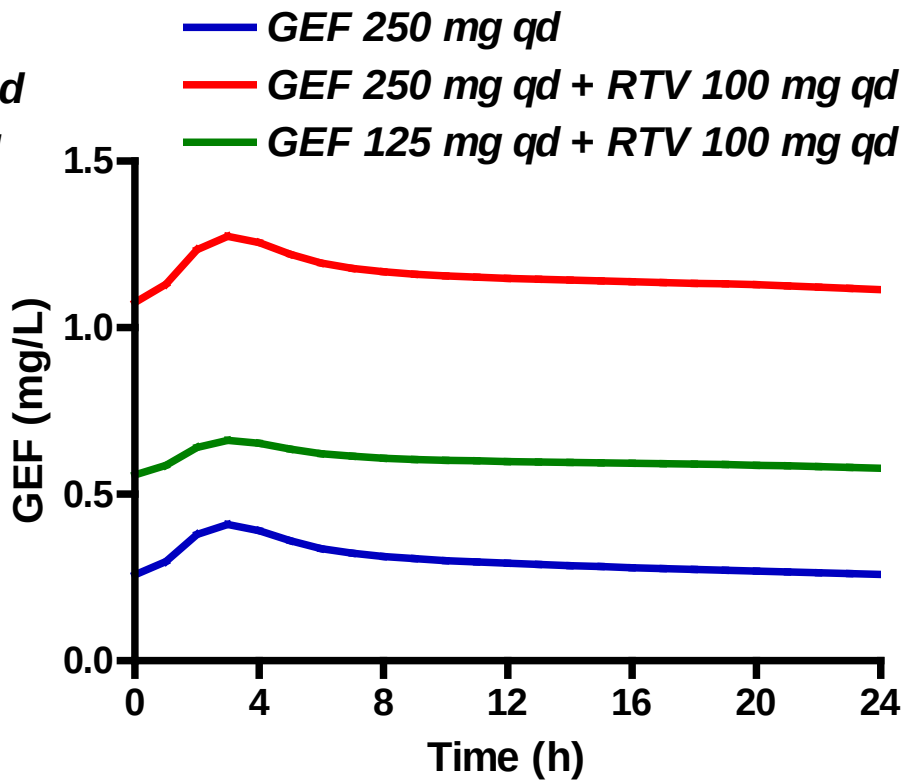


GMR (90%CI)	ERL 150mg qd + RTV 100mg qd (vs ERL 150mg qd)
AUC_{0-24}	4.53 (4.11 - 4.99)
C_{max}	3.79 (3.48 - 4.14)

GMR (90%CI)	GEF 250mg qd + RTV 100mg qd (vs GEF 250mg qd)
AUC_{0-24}	3.85 (3.62 – 4.09)
C_{max}	3.12 (2.96 – 3.29)

Dose adjustment for ERL/GEF + RTV

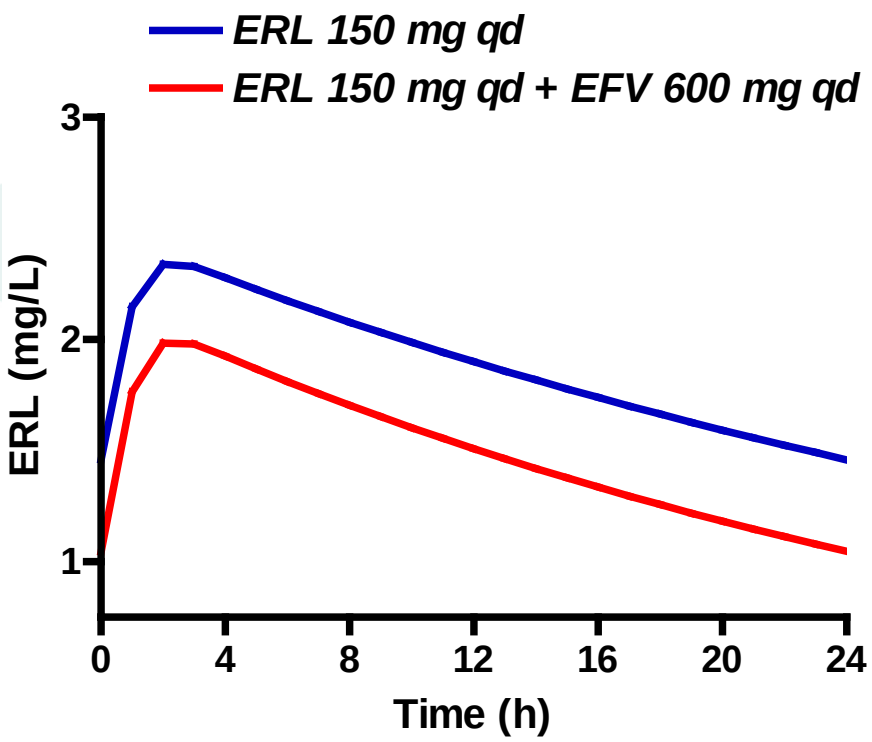


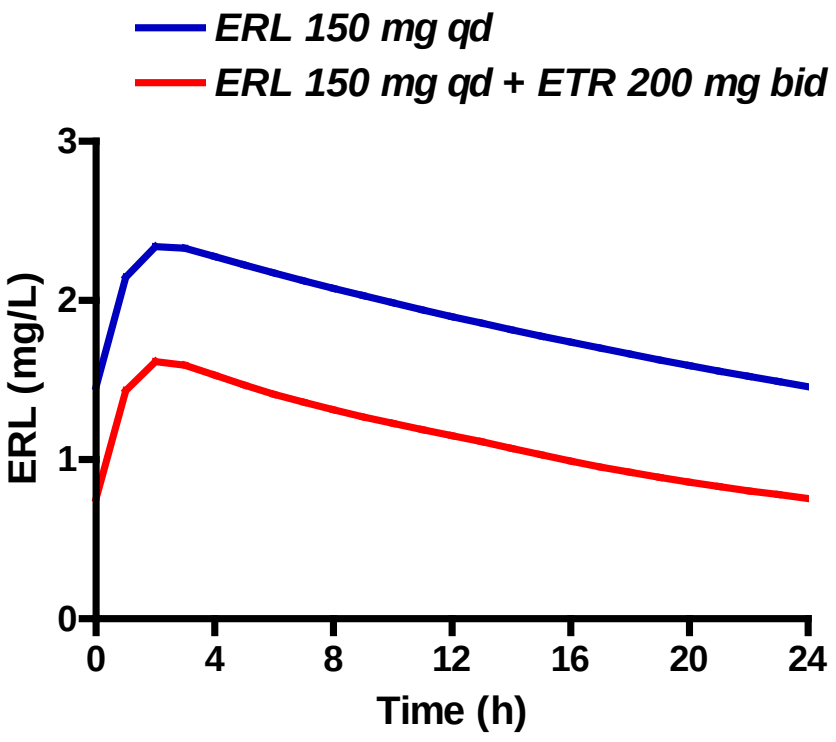


GMR (90%CI)	ERL 25mg qd + RTV 100mg qd (vs ERL 150mg qd)
AUC_{0-24}	0.72 (0.66 – 0.79)
C_{max}	0.61 (0.56 – 0.66)

GMR (90%CI)	GEF 125mg qd + RTV 100mg qd (vs GEF 250mg qd)
AUC_{0-24}	1.99 (1.86 – 2.13)
C_{max}	1.61 (1.52 – 1.71)

Erlotinib & EFV/ETR

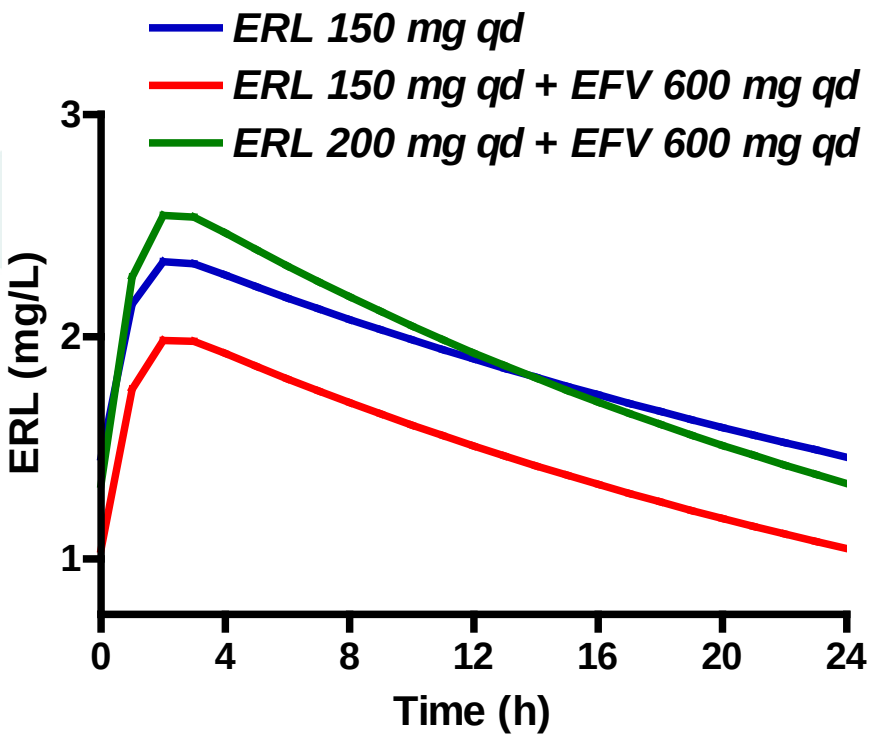


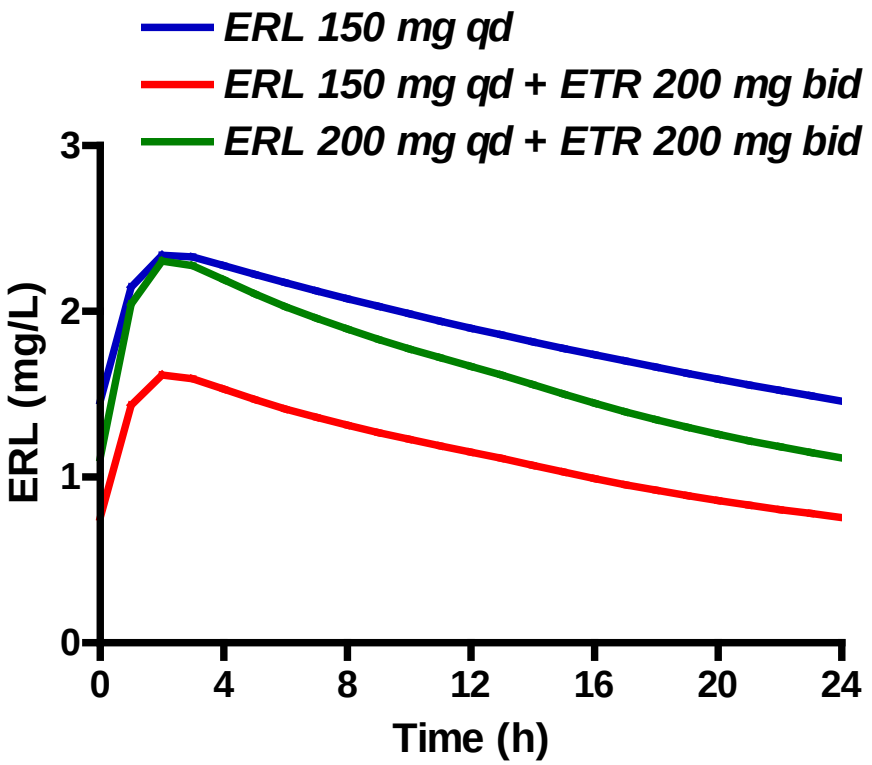


GMR (90%CI)	ERL 150mg qd + EFV 600mg qd (vs ERL 150mg qd)
AUC_{0-24}	0.85 (0.76 – 0.95)
C_{max}	0.89 (0.82 – 0.97)

GMR (90%CI)	ERL 150mg qd + ETR 200mg bid (vs ERL 150mg qd)
AUC_{0-24}	0.60 (0.55 – 0.66)
C_{max}	0.69 (0.64 – 0.74)

Dose adjustment for ERL + EFV/ETR

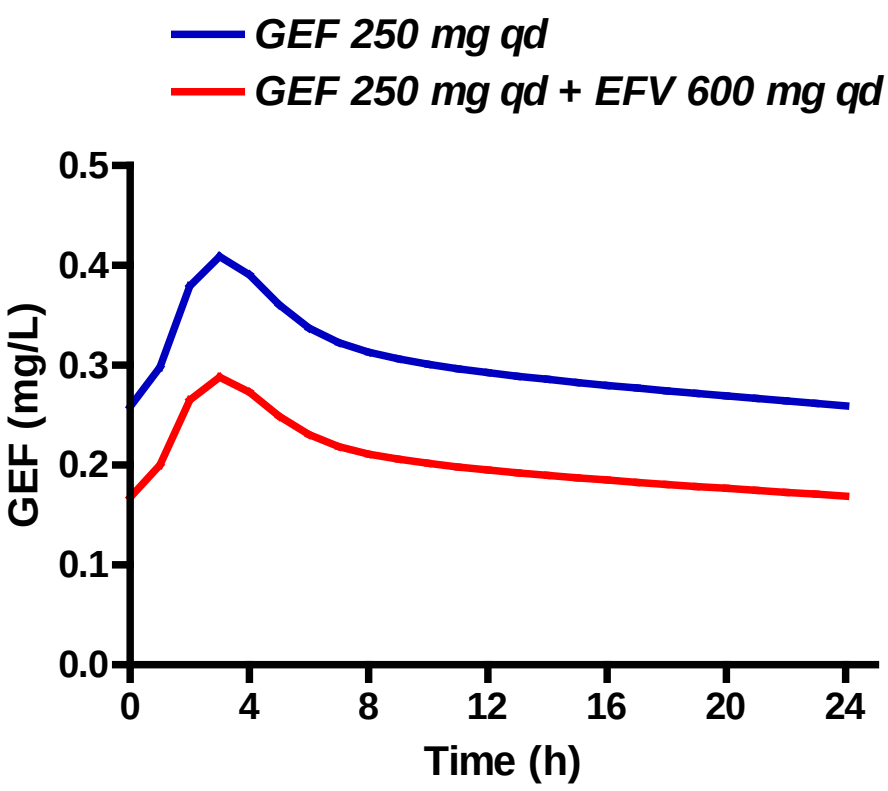




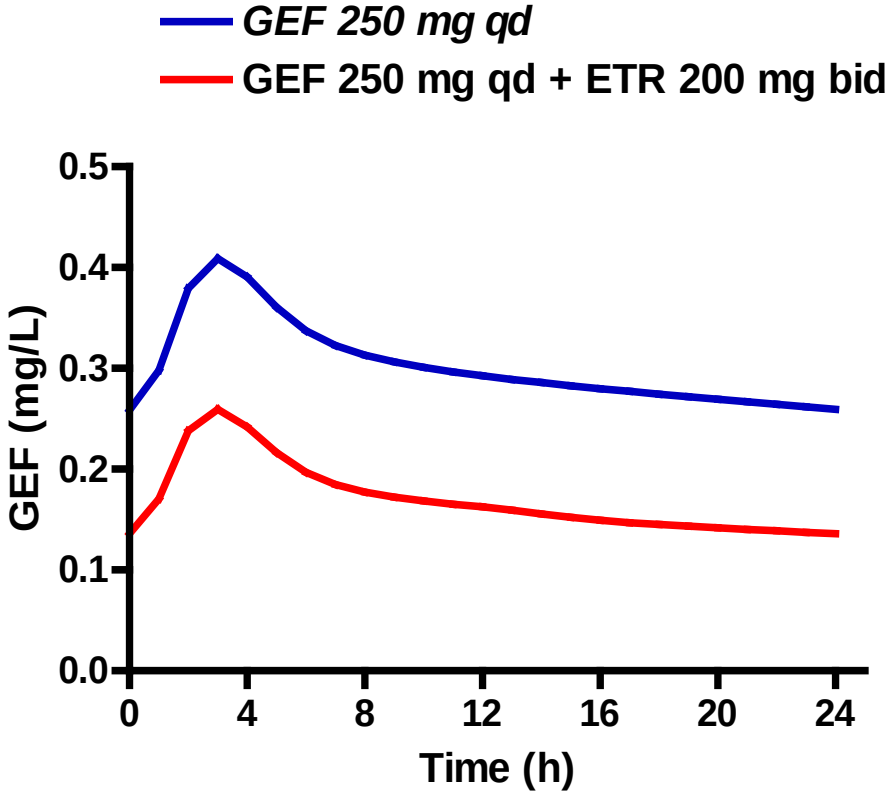
GMR (90%CI)	ERL 200mg qd + EFV 600mg qd (vs ERL 150mg qd)
AUC_{0-24}	1.07 (0.96 – 1.20)
C_{max}	1.14 (1.04 – 1.24)

GMR (90%CI)	ERL 200mg qd + ETR 200mg bid (vs ERL 150mg qd)
AUC_{0-24}	0.89 (0.82 – 0.96)
C_{max}	0.99 (0.93 – 1.06)

Gefitinib & EFV/ETR

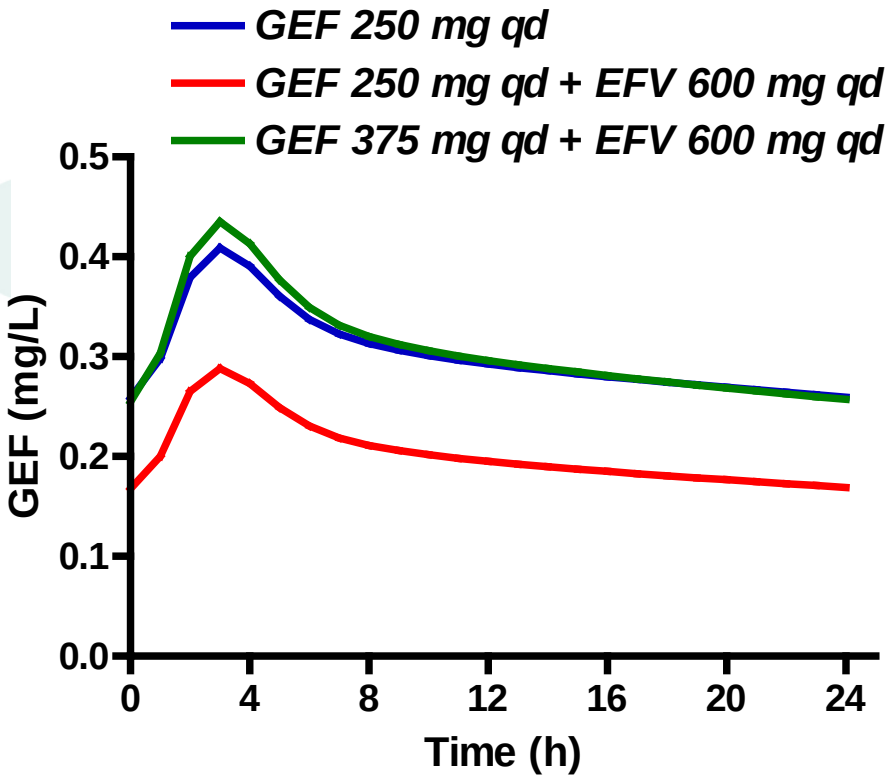


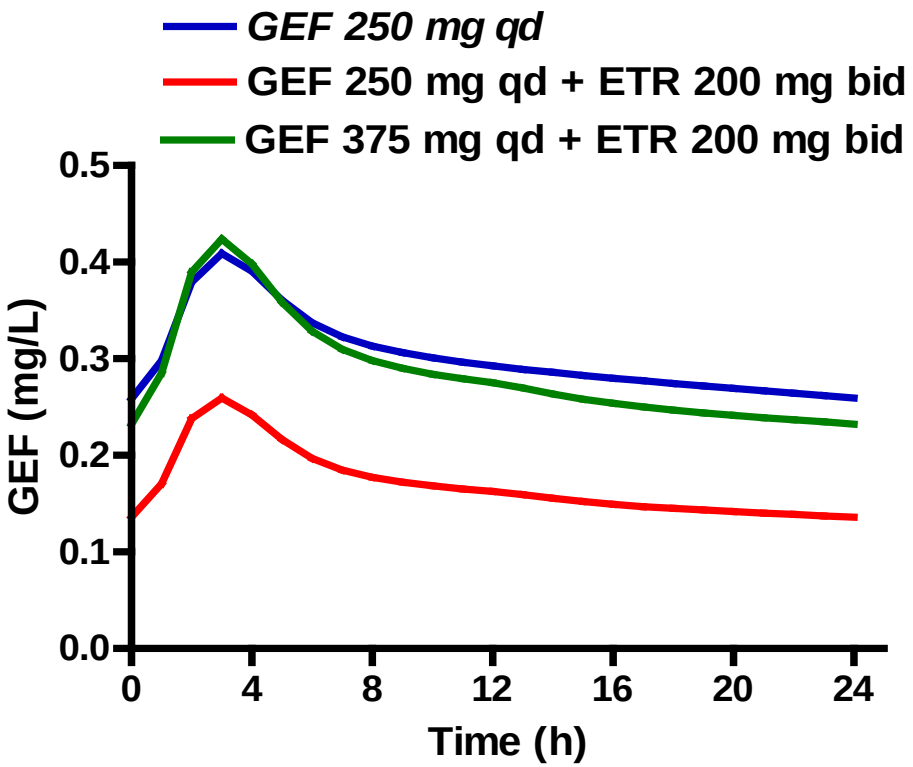
GMR (90%CI)	GEF 250mg qd + EFV 600mg qd (vs GEF 250mg qd)
AUC_{0-24}	0.67 (0.60 – 0.75)
C_{max}	0.71 (0.65 – 0.77)



GMR (90%CI)	GEF 250mg qd + ETR 200mg bid (vs GEF 250mg qd)
AUC_{0-24}	0.64 (0.58 – 0.71)
C_{max}	0.70 (0.65 – 0.76)

Dose adjustment for GEF + EFV/ETR





GMR (90%CI)	GEF 375mg qd + EFV 600mg qd (vs GEF 250mg qd)
AUC_{0-24}	1.02 (0.90 – 1.04)
C_{max}	1.07 (0.98 – 1.16)

GMR (90%CI)	GEF 375mg qd + ETR 200mg bid (vs GEF 250mg qd)
AUC_{0-24}	1.08 (0.98 – 1.19)
C_{max}	1.15 (1.06 – 1.24)

Conclusions

- The developed PBPK model predicted the *in vivo* pharmacokinetics of ERL or GEF, and their interactions with RTV, EFV or ETR.
- Potential simulated dose adjustments in that scenario

	Alone	+ RTV 100 mg qd	+ EFV 600 mg qd +ETR 200 mg bid
ERL	150 mg qd	25 mg qd	200 mg qd
GEF	250 mg qd	125 mg qd	375 mg qd

- The simulated dose-adjustments may represent valuable strategies to optimise antineoplastic therapy in HIV patients receiving cART.
- The PBPK approach may be a useful tool for both prediction of DDI and selection of doses to explore in prospective clinical trials.

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